Journal of Surgical Oncology 1999;71:32–35

Prognostic Factors in Retroperitoneal Sarcomas: Ploidy of DNA as a Predictor of Clinical Outcome

KRZYSZTOF HERMAN, MD, PhD,[1]* ANDRZEJ GRUCHAŁA, MD, PhD,[2] ALEKSANDER NIEZABITOWSKI, MD, PhD,[2] BOGDAN GLIŃSKI, MD, PhD,[3] AND BOŻENA LACKOWSKA[2]

[1]*Department of Surgical Oncology, Cancer Centre, Marie Sklodowska-Curie Memorial Institute of Oncology, Kraków, Poland*

[2]*Department of Pathology, Cancer Centre, Marie Sklodowska-Curie Memorial Institute of Oncology, Kraków, Poland*

[3]*Department of Radiotherapy, Cancer Centre, Marie Sklodowska-Curie Memorial Institute of Oncology, Kraków, Poland*

Background and Objectives: Radical surgery is the best mode of treatment of retroperitoneal sarcomas (RS); however, common recurrences are unpredictable.

Methods: For the better understanding of outcomes and possibilities of treatment retrospective analysis of different factors, including DNA content, was performed based on 70 patients.

Results: Leiomyosarcoma and liposarcoma were most common histologic types of classified sarcomas. Different kinds of resection were successfully performed in 51 patients (73%) and 35 of their available DNA specimens were analyzed. The actuarial 5- and 10-year survival rates in the resection group were 53% and 40%, respectively, with the median survival of 57 months. Patients with diploid resected tumors had a better 10-year survival rate (58%), than those patients with aneuploid tumors (25%,)—$P < 0.005$. Those patients with low-grade sarcomas had a significantly longer survival than those with high-grade sarcomas (10-year survival rate: 44% compared to 29%). In the univariate analysis, adjuvant therapy, type of histology, type of surgery, location of tumor, and S-phase fraction had no influence on survival. In the multivariate analysis (Cox), only ploidy was an independent prognostic variable. Relative risk of death was over three times higher for aneuploid than for diploid tumors.

Conclusion: Tumor ploidy should be analyzed in every case of retroperitoneal sarcoma for better assessment of prognosis and possible indication for adjuvant therapy. *J. Surg. Oncol. 1999:71:32–35.*

KEY WORDS: **retroperitoneal sarcoma; ploidy; prognostic factors**

INTRODUCTION

Soft tissue sarcomas are rare malignant tumors, and 10–20% of them are located in retroperitoneal space [1]. In Poland, approximately 100 new cases of retroperitoneal sarcomas (RS) are diagnosed annually, and therefore only a few centers could attain some experience in this field. The slow-growth and little or no symptoms lead to the usually large size of the tumors. More than 15 different histologic types, different grading, and the uncommon incidence of these tumors make any comparison difficult, and conclusions doubtful. Radical surgery is the best mode of treatment; however, the full histological assessment of tumor borders margins in giant malignan-

*Correspondence to: Krzysztof Herman MD, PhD, Cancer Centre ul. Garncarska 11, 31-115 Kraków, Poland. Fax No.: (48) 12-423-1595. E-mail: hermank@polbox.com

Accepted 5 December 1998

cies is often difficult. The phrase "radical excision" means something quite different in different data (from simple excision and extirpation to so-called "en-block" resection), therefore there is no possibility to compare results from various hospitals [2]. The unresectability and local failure rates are very high (30% and 50%, respectively). Only one author had a 100% rate of resectability for primary tumors, and only a 25% rate of local recurrence [3]. It is well known that histological grading and completeness of surgery influence survival chances [1], but there is little information about other prognostic factors. We have not found in the literature any data on the value of DNA content assessment in RS. Therefore, for better understanding of the prognosis of sarcomas in this location, we calculated the importance of different clinical and pathological variables, including ploidy of DNA.

PATIENTS AND METHODS

Seventy patients with retroperitoneal sarcomas were treated at the Cancer Centre in Kraków from 1965 to 1994. Their medical records were reviewed to determine the clinical presentation, and their pathological specimens were reanalyzed to assess histological type and grading. In 35 specimens available in our institution, DNA content in paraffin material was measured using the Hedley technique [4]. The tumors were graded according to the systems of Enzinger (G1–3). By the end of 1996, all patients had a minimum follow-up of 2 years. Survival data were assessed according to the Kaplan-Meier life-table method, and prognostic variables were evaluated in multivariate analysis with Cox's regression model. *P*-value was regarded as significant at $P < 0.05$).

There were 34 females and 36 males, with a mean age of 48 (range, 28–76) years. Average duration of symptoms was 7 months. The most common symptoms were pain and discomfort presented in 46 cases, and abdominal mass in 38. Thirty-seven patients were referred to our Centre with previously untreated primary tumors, 15 had earlier nonradical surgery or exploration, and the others (18) had recurrent tumors. Full data concerning follow-up were available for all patients. There is no information of the certain cause of death in eight patients who died in the dissemination period.

RESULTS

Types of surgical treatment are presented in Table I. Three patients died in the perioperative period, including one intraoperative death due to cardiac arrest following massive intraoperative bleeding. Tumor resection was possible in 51 of 70 patients (73%), with a histologically proven radicality rate of 53% (in 27 of 51 patients). In all patients, 112 operations have been performed for primary and recurrent tumors with a maximum of seven operations per patient. The mean diameter of tumor was 18 cm (range, 5–32). Most common histological types were leiomyosarcoma (23%), liposarcoma (20%), malignant fibrous histiocytoma (14%), and schwannoma (13%) (Table II). High-grade (25 cases) and moderate-grade sarcomas (33 cases) were more frequent than low-grade tumors (12 cases). Of the available specimens, DNA content analysis showed 20/35 aneuploid (57%) and 15/35 diploid (43%) tumors. Adjuvant therapy, including different modes of chemotherapy and/or external radiotherapy (20–50 Gy) was performed in 36 patients.

TABLE I. Type of First Surgical Treatment of Retroperitoneal Sarcomas*

Type of surgery	Number of patients	Percentage
Without resection (exploration only)	19	27%
Partial resection	4	6%
Radical resection	37	53%
Extended resection (including adjacent organs)	10	14%
Total	70	100%

*Based on surgeon's assessment (n = 70).

The actuarial 5-year and 10-year survival rates in the group of patients after tumor resection is 53% and 40% (respectively) with a median survival of 57 months (compared to 10 months without resection). The maximal survival in one patient without tumor removal was 34 months (Fig. 1). Patients with low- or moderate-grade of sarcoma had significantly ($P = 0.037$) longer survival, than with high-grade (10-year survival rate 44%, compared with 29%) (Fig. 2). The survival data of our patients with available specimens and DNA content analysis showed 58% 10-year survival for diploid tumors and 25% for aneuploid ($P = < 0.00285$) (Fig. 3). Although patients without adjuvant therapy had a better survival rate (Fig. 4), these results were not significant ($P = 0.46$). We have to emphasise that only patients with clinically more advanced disease and/or with high-grade tumor were qualified for adjuvant therapy. There was no influence on survival of other factors, such as location of tumor, duration of symptoms, histological direction of tumor's differentiation, type of tumor resection, or S-phase percentage in univariate analysis.

In the multivariate analysis (Cox), only ploidy was an independent prognostic variable for survival. Relative risk of death was over three times higher for aneuploid than for diploid tumors. High grading was correlated with bad prognosis, and relative risk of death for nondifferentiated sarcomas was 2.5 times higher than for others. However, these results were not significant (Table III). Other variables used in analysis, such as adjuvant treatment, size of tumor, histological margins, S-phase fraction, or type of histology had no influence on survival.

TABLE II. Histological Type of Retroperitoneal Sarcomas*

Histological type	Number of patients	Percentage
Leiomyosarcoma	16	22.8%
Liposarcoma	14	20%
Malignant fibrous histiocytoma	10	14.3%
Schwannoma	9	12.9%
Haemangiopericytoma	3	4.3%
Rhabdomyosarcoma	1	1.4%
Other or nonclassified	17	24.3%
Total	70	100.0%

*n = 70.

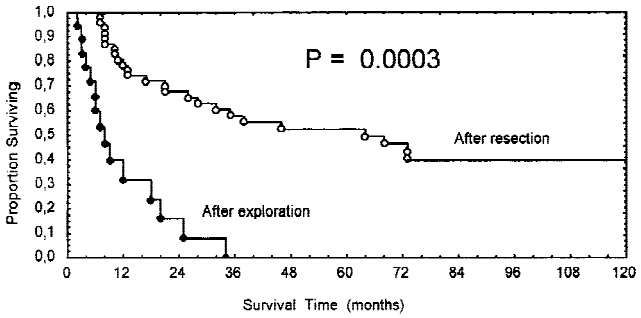

Fig. 1. Total survival in retroperitonal sarcomas—comparison of the types of surgery.

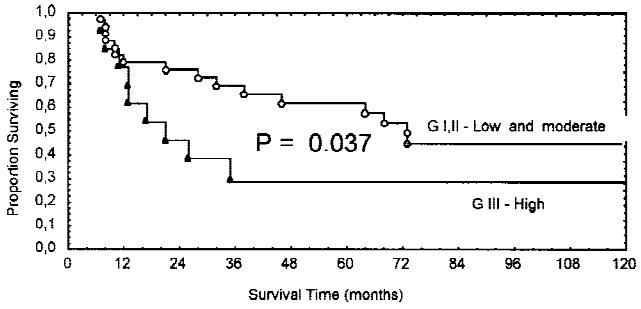

Fig. 2. Total survival after resection of the retroperitoneal sarcomas—comparison of low- and moderate-, and high-grade groups.

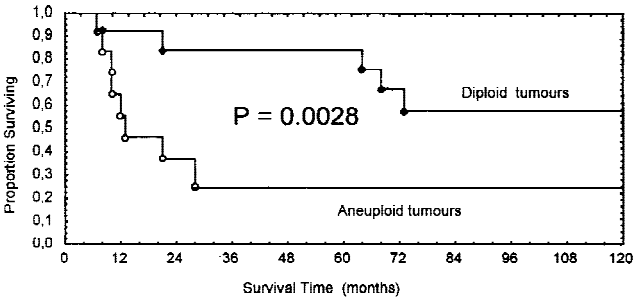

Fig. 3. Total survival after resection of retroperitoneal sarcomas—comparison of diploid and aneuploid tumors.

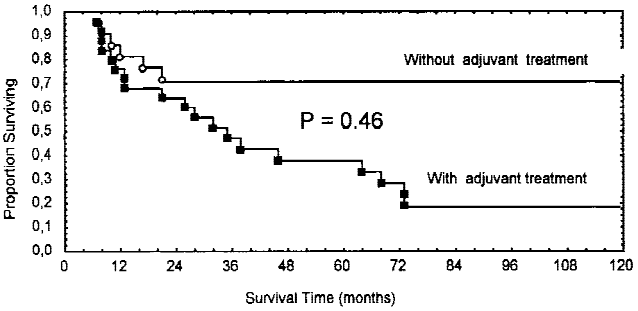

Fig. 4. Total survival after resection of retroperitoneal sarcomas—the role of adjuvant treatment.

TABLE III. Influence of Independent Variables on Survival—Relative Risk of Death (RR) in Patients After Tumor Resection†

Prognostic factor	Standard error	*P*-value	RR
Ploidy aneuploid/diploid	0.5518	0.0387*	3.128
Grading high/moderate and low	0.5191	0.074*	2.520
Adjuvant therapy yes/no	0.1284	0.885*	1.018
Histological margins positive/negative	0.0170	0.746*	0.994
S-phase fraction	0.1588	0.961*	0.9924
Type of histology	0.0497	0.281*	0.9478
Tumor size (<10 cm>)	0.5614	0.399*	0.6229

†n = 35, including DNA examination, excluding perioperative deaths.
*Not significant.

DISCUSSION

Retroperitoneal sarcomas remain a clinical and pathological challenge. The results of chemotherapy and radiotherapy were discouraging in most other series [5,6], as well as in our data. Lately, published articles are more stimulating with adjuvant [7,8] or neoadjuvant [9] therapy for RS . Similarly, a pilot study from Bordeaux [10] with intraoperative radiation therapy for RS is very interesting. However, there is no agreement as to when and what kind of adjuvant therapy should be given for which tumors.

Flow cytometric DNA measurements have proven to be helpful in evaluating some types of tumor. In soft tissue sarcomas, the available data are contradictory [11–13]. The literature reports a wide range of percentages of aneuploidy in other than theRS retroperitoneal location, depending on histological types, from 26% to 87% [14,15]. In our series, there were 57% aneuploid tumors, but we did not find any other correlation with histology. Based on multivariate analysis, tumor ploidy appeared to be the only one significant, independent prognostic factor for the risk of mortality in the whole group of RS patients. Grading, of course, seems to play an important role for the RS prognosis; however, our material has not confirmed this fact conclusively, probably due to the small number of patients. To our surprise, completeness of surgery and histological margins did not influence risk of deaths in our patients. Shiloni et al. have made the

same observations [16].We have no other explanation for such phenomena than the insufficient number of analyzed cases.

Some authors find S-phase fraction to be an independent prognostic factor in soft-tissue sarcomas [17]; however, it has not been confirmed in these data including only RS. The previous data from our institution showed that MIB-1 index was strongly correlated with the sarcoma's grade and independently influenced overall survival [18].

CONCLUSION

In retroperitoneal sarcomas, not only the grading—but also the DNA ploidy—seem to be important, independent prognostic factors influencing survival. We believe that there is a great need for prospective multiinstitutional analysis to solve two main problems in RS: (1) which tumors are associated with a worse prognosis; and (2) when and what kinds of adjuvant or neoadjuvant therapy should be given to patients with these worse prognostic factors.

REFERENCES

1. Singer S, Corson JM, Demetri GD, et al.: Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma. Ann Surg 1995;22:185–195.
2. Storm FK, Mahvi DM: Diagnosis and management of retroperitoneal soft-tissue sarcoma. Ann Surg 1991;214:2–10.
3. Karakousis CP, Velez AF, Gerstenbluth R, Driscoll DL: Resectability and survival in retroperitoneal sarcomas. Ann Surg Oncol 1996;3:150–158.
4. Hedley DW, Friedlander ML, Taylor IW, et al.:, Rugg CA, Musgrove EA. Method for analysis of cellular DNA content of paraffin-embedded pathological material using flow cytometry. J Histochem Cytochem 1983;31:1333–1335.
5. Jaques DP, Coit DG, Hajdu SI, Brennan MF: Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum. Ann Surg 1990;212:51–59.
6. Cody HS, Turnbull AD, Fortner JG, Hajdu SI: The continuing challenge of retroperitoneal sarcomas. Cancer 1981;47:2147–2152.
7. Sugarbaker PH: Early postoperative intraperitoneal Adriamycin as an adjuvant treatment for visceral and retroperitoneal sarcoma. Cancer Treat Res 1996;81:7–14.
8. Fein DA, Corn BW, Lanciano RM, et al.: Management of retroperitoneal sarcomas: Does dose escalation impact on locoregional control? Int J Radiat Oncol Biol Phys 1995;31:129–134.
9. Robertson JM, Sondak VK, Weiss SA, et al.: Preoperative radiation therapy and iododeoxyuridine for large retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys 1995;31:87–92.
10. Bussiers E, Stockle EP, Richaud PM, et al.: Retroperitoneal soft tissue sarcomas: A pilot study of intraoperative radiation therapy. J Surg Oncol 1996;62:49–56.
11. Kilipatrick SE, Teot LA, Geisinger KR, et al.: Relationship of DNA ploidy to histology and prognosis in rhabdomyosarcoma. Cancer 1994;74:3227–3233.
12. Pastel-Levy C, Bell DA, Rosenberg AE: DNA flow cytometry of epithelioid sarcoma. Cancer 1992;70:2823–2826.
13. Budach W, Budach V, Socha B, et al.: DNA content as a predictor of clinical outcome in soft tissue sarcoma patients. Eur J Cancer 1994;30A:1815–1821.
14. Oshiro Y, Fukuda T, Tsuneyoshi M, et al.: Fibrosarcoma versus fibromatoses and cellular nodular fascitis. A: A comparative study of their proliferative activity using proliferating cell nuclear antigen, DNA flow cytometry and p53. Am J Surg Pathol 1994;18: 712–719.
15. Xiang J, Spanier SS, Benson NA, Braylan RC: Flow cytometric analysis of DNA in bone and soft-tissue tumors using nuclear suspensions. Cancer 1987;59:1951–1958.
16. Shiloni E, Szold A, White DE, Freund HR: High-grade retroperitoneal sarcomas: Role of an aggressive palliative approach. J Surg Oncol 1993;53:197–203.
17. Collin F, Chassevent A, Bonichon F, et al.: Flow cytometric DNA content analysis of 185 soft tissue neoplasms indicates that S-phase fraction is a prognostic factor for sarcomas. Cancer 1997; 79:2371–2379.
18. Niezabitowski A, Ryoles J, Roessner A, et al.: Assessment of proliferative activity, DNA values and some clinicopathologic parameters in mesenchymal tumors. Gen Diagn Pathol 1996/97;142: 327–333.